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Editorial

Dopaminergic augmentation of restless legs syndrome: The scope of the problem

Dopaminergic agents have been used for the treatment of RLS for nearly 30 years [1]. Their short- and mid-term efficacy is now well established, and for most non-ergot derivatives, open label long-term studies have been performed for periods of up to a year. The side effects of these agents are generally mild and transient and, in contrast to their use in Parkinson's disease, no cases of dyskinesias have been reported [2–4]. There is, however, a long-term complication encountered with dopaminergic therapy: treatment-related augmentation of RLS symptoms [5].

Augmentation was initially described as a worsening of symptom severity during long-term treatment with levodopa [6]. A characteristic feature of the disorder was that the severity of symptoms was actually worse than before initiation of treatment, and improved when the medication was discontinued. Such worsening of symptom severity was manifested by an earlier onset of symptoms in the afternoon or evening (100% of patients), a quicker onset of symptoms following rest (56%), an increased intensity of symptoms (96%), a spread of symptoms to different body parts (11%), and a shorter duration of the effect of the medication [8]. Augmentation was severe enough to require a change in medication in approximately 50% of the patients.

Although the condition was initially described during treatment with levodopa, subsequent studies have found augmentation with all dopaminergic agents [5]. However, in the absence of clear diagnostic criteria (clinical definitions varied widely) and sufficiently long prospective studies, incidence rates of augmentation have been frequently unreliable or even not provided at all. In an effort to standardize and universalize clinical recognition of augmentation, the NIH-sponsored RLS Diagnosis and Epidemiology Workshop defined clinical criteria for augmentation in 2003 [7]. These were further improved in 2006 at an international symposium organized at the Max-Planck Institute in Munich [8] that used empirical information yielded by specific clinical studies.

Both the NIH and Max Planck Institute diagnostic criteria have been used over the last years in several, large scale, multicenter studies [9–11] with results only partially published at the time of writing.

A conservative application of these diagnostic criteria has shown small incidence rates over periods of up to 6 months. It is possible that the use of low doses of dopaminergic agents might have resulted in an increased number of cases of loss of efficacy/tolerance instead of augmentation and that loss of efficacy might reflect an initial stage leading to augmentation if treatment is continued [12]. Hence, in an effort to identify augmentation in its early stages, the International Restless Legs Study Group has recently developed operational criteria to define loss of efficacy in clinical trials [13].

The question is whether these rates would grow with longer treatment duration, especially since treatment of RLS is frequently lifelong. Recent data suggest that the incidence rate of augmentation affects more severely a growing number of patients over time. Thus, a 10-year follow-up study of patients on dopamine agonists showed modest (5–7%) but constant annual rates of new cases with augmentation that persisted without significant change over the study period. In this study, augmentation did not abate but required discontinuation of dopaminergic treatment after 5 years in 42–65% of the subjects [14].

As all of the previous studies on augmentation were performed in research settings or in specialized clinics, it could be argued that these RLS populations represent a subsample of patients that are resistant to conventional treatments, and are hence not representative of the common RLS population. A study published by Allen et al. [15], in this issue of *Sleep Medicine* provides evidence of the contrary. The authors performed an online survey of 266 patients being treated mainly by their primary care physicians or neurologists in a large number of practices across the USA. In this sample, 20% of the patients provided reports that according to NIH criteria were classified as definite or highly suggestive of augmentation. A further 56% were classified as possible augmentation and only 25% of the patients reported no indications of augmentation at all. New cases of RLS augmentation occurred at a rate of 8% each year for at least the first 8 years of dopaminergic treatment. Patients presenting with definitive or highly suggestive augmentation were the least satisfied with their treatment, reported the most severe RLS symptoms (with an average IRLS total score of 23.6), experienced the greatest degree of sleep disturbance and suffered the most substantial reduction in quality of life due to RLS.

Taken together, increasing evidence supports the view that augmentation represents a major challenge to the long-term treatment outcome when dopaminergic agents are used, whether in primary care or in specialized clinics. It is possible that dopaminergic agents might vary between each other in the rate at which new patients are affected over time. In any case this should raise concern as it would imply a slowly growing number of patients for which RLS severity could worsen, even if the speed at which augmentation occurs might vary somewhat for the various dopaminergic agents. Clearly, it seems important to look at longer-term clinical data on all dopaminergic drugs to evaluate this possibility.

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Conflict of Interest

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